# THE ANOXIA TEST FOR MYOCARDIAL ISCHÆMIA

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When the symptoms are typical, the diagnosis of angina pectoris is relatively easy, even in the absence of objective signs of cardiovascular disease. Nevertheless, Evans (1952) pointed out that where this objective evidence is missing the diagnosis of angina pectoris is likely to be wrong in one out of every four cases. Biorck (1946) stated that he could be certain of the diagnosis in only one out of every six patients who had been thought to have angina pectoris.

To help in difficult cases, where objective evidence of coronary insufficiency cannot be found or relied upon, four types of special tests have been designed to produce electrocardiographic evidence of coronary insufficiency. Levine *et al.* (1930) introduced the adrenaline test, and Ruskin (1947) the pitressin test, but both have been abandoned for general use, as they are potentially harmful. The exercise test has been widely used and developed (Master *et al.*, 1935 and subsequently, Evans and Bourne (1941), Twiss and Sokolow (1942), Biorck (1946), Wood *et al.* (1950) and many others). Unfortunately, there has been no general agreement as to what constitutes positive evidence of coronary insufficiency in this test, and this makes assessment of its value a little difficult.

The fourth method by which evidence of coronary insufficiency can be demonstrated is by the production of general anoxia by inhalation of a low-oxygen gas mixture, and recording electrocardiograms at certain intervals. Extensively investigated by Levy and his co-workers (1938, 1939, etc.) by Patterson *et al.* (1942), and Mathers and Levy (1950, 1952), the test produced a positive result in only half of the patients with known coronary insufficiency. However, Levy's three criteria of positiveness in the test have been universally used and have formed the basis of all subsequent work in this field: they were as follows.

1. The arithmetical sum of the RS–T segment deviation in the three standard leads and the præcordial lead totals 3 mm. or more, when 1 cm. deflection is equivalent to 1 millivolt.

2. There is partial or complete reversal of the T wave, with RS–T segment deviation of 1 mm. or more, in lead I.

3. There is complete reversal of the T wave in the præcordial lead.

Malmstrom (1947) modified the method of performing the test by reducing the concentration of oxygen in the inhaled gas mixture and added carbon dioxide, successfully increasing the number of positive results in patients with coronary insufficiency, without producing abnormal records in patients where this insufficiency did not exist. His series of patients was small in number, however. This paper is concerned with the findings and personal observations in a larger series of patients upon whom Malmstrom's modification of Levy's anoxia test was performed.

## METHOD OF APPLICATION

To induce anoxia, Levy and his associates used a mixture of 10 per cent oxygen and 90 per cent nitrogen, but for reasons that will be discussed later, Malmstrom employed a mixture of 6·5 per

cent oxygen, 4·5 per cent carbon dioxide, and 89 per cent nitrogen. A similar mixture was used throughout this series, using a standard Walton anæsthetic machine.

The mixture of gas is delivered to the patient through a system of flutter valves to prevent re-breathing, and an emergency supply of oxygen is ready to be introduced into the circuit if necessary. The gas can be inhaled by the patient either through a standard anæsthetic face piece or through a mouthpiece, using a nose clip to prevent nasal breathing.

All patients in this series were seen and examined by the author, before the test was performed. The object of the test and its method were fully explained to each patient, and any undue apprehension or reluctance to undergo the test was sufficient reason for it not to be used. This was not only for the sake of safety, but because it has been shown that fright in itself is sufficient to produce electrocardiographic changes (Mainzer and Krause, 1940). No vasodilator drugs were given for twelve hours before the test, and only one case was being treated with digitalis. The test was performed at least two hours after the last meal, and after the patient had been at rest for at least half an hour. Instructions were given that any discomfort experienced during the test other than moderate dyspnœa, should be signalled by raising an arm, when the test would be stopped. For convenience, all the tests were performed with the patient semi-recumbent on a couch, no alteration of the position being allowed. All the electrocardiograms were recorded on a direct-writing instrument, the tracings being thus available for immediate inspection.

A full twelve-lead electrocardiogram was recorded before the test was begun, the chest lead to be chosen for use during the test being that with the tallest R and the smallest S, this lead being assumed to be over the maximum thickness of the left ventricle. With all the preliminaries completed, the mouth piece or face piece was applied and the patient allowed to breathe room air for a few minutes to become accustomed to the apparatus. The gas mixture was then introduced, a constant flow being kept up during the test. Records were originally taken at five, ten, fifteen, and twenty minutes anoxia, but it was soon realized that prolongation of the test beyond ten minutes was unnecessary, positive results often occurring within the first few minutes. Finally, therefore, the technique evolved was to record electrocardiograms at two, five, seven, and ten minutes, then after the inhalation of oxygen for one minute, and again after five minutes rest, repeating the recording at five minute intervals until the tracing returned to the resting state. If the patient signalled the presence of discomfort or if the records showed notable change, the anoxia was stopped, an electrocardiogram taken, oxygen given for one minute, and further recordings made as described above. The three standard leads of the electrocardiogram, and one chest lead, were recorded at each interval, and with practice it was found possible to complete each set of tracings well within thirty seconds. No patient had the test performed if there was any suspicion of myocardial infarction having occurred within the previous four months. Other conditions precluding the test were congestive cardiac failure, obvious illness of the patient, severe anæmia, and a high degree of pulmonary disease. The exercise test was done according to the method of Wood *et al.* (1950).

The interpretation of the electrocardiograms was based upon Levy's work, and it was confirmed that RS–T segment changes were the most important findings. Compared with the control group, no significant alterations occurred in the heart rate, the P waves, and the QRS complexes, and significant arrhythmias occurred in only two patients. The measurement of RS–T segment deviation was made in each lead by taking the average of five successive complexes. The iso-electric level was taken as the P–Q interval, or the point before the first deflection of the QRS complex, as recommended by Levy (above), Malmstrom (1947), Katz (1946), and Master (1953). The T–P level was impractical, since the tachycardia found in many of the tests obliterated this interval. The RS–T segment level was taken as the point when this interval began. The arithmetical sum of RS–T segment deviation in all four leads could then be found.

RESULTS

One hundred and eleven patients were examined, 126 anoxia tests being performed. Eleven exercise tests were performed for comparison with the anoxia test. The follow-up period varied

from eighteen months to three years, during which time six of the patients died, autopsies being performed on three.

To simplify observation and assessment, the patients were divided into four groups.

*Group 1* was made up of 41 patients with no clinical evidence of organic cardiovascular disease, and served as a control.

*Group 2* included 53 patients in whom coronary artery insufficiency was suspected on clinical grounds.

*Group 3* comprised 7 patients with peripheral arterial disease causing symptoms of intermittent claudication, but without symptoms of angina pectoris.

*Group 4* was a miscellaneous group of 10 patients.

The distribution of cases in Group 1 and in Groups 2, 3, and 4 combined, as regards age and sex, was approximately equal.

Twenty-five tests on twenty-one patients were abandoned before the test could be completed. The main reasons for this failure were fear of the test in twelve cases, and intolerable dyspnœa in eleven. Fear amounting to panic was probably the result of inadequate explanation of what was happening, and rarely occurred as experience in the use of the test by the operator increased. All the patients in whom dyspnœa caused the test to be stopped had clinically recognizable pulmonary emphysema.

Constricting chest pain exactly similar to anginal pain occurring on effort was present in 17 of the tests. Electrocardiograms taken at the time of the pain showed positive results in 16. The only case where no significant cardiographic change occurred had previously shown a positive test. On the other hand, the test was stopped on 15 occasions because of striking alteration in the electrocardiogram without the occurrence of any discomfort whatsoever, one of these patients having a total RS–T segment deviation of 11·0 mm. This experience is in line with that of other observers, in that pain and cardiographic change are not always concurrent; it is uncommon to have pain without cardiographic change, but not vice versa. Twenty-three patients had the tests stopped because of such changes but admitted later to having very minor degrees of chest discomfort. When the pain complained of was not typically cardiac, as happened in three instances, there was no cardiographic change. In all the other cases pain was immediately relieved by the administration of oxygen, although the return of the cardiogram to the resting state was invariably much less rapid, in some cases taking up to fifteen minutes.

Table I lists the types of reaction to the test observed in this series, although not all these reactions caused the test to be abandoned. Headache was described as bursting, but was relieved at once by

TABLE I

REACTIONS TO THE ANOXIA TEST

|  | Number of times observed | Number of patients |
|---|---|---|
| Fear .. .. .. .. .. | 19 | 16 |
| Intense dyspnœa .. .. .. .. | 21 | 20 |
| Chest pain, cardiac type .. .. | 18 | 16 |
| Chest pain, non-cardiac type .. .. | 5 | 5 |
| Headache .. .. .. .. .. | 3 | 3 |
| Blurred vision .. .. .. .. | 1 | 1 |

oxygen, as was the one example of blurred vision. None of the reactions to the test produced any permanent ill effects.

Table II summarizes the results in the whole series of completed tests. For purposes of more detailed analysis, group 2, clearly the most important, has been broken down into further subgroups, A, B, C, and D. Group A included ten patients where coronary artery disease was known to exist,

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TABLE II
Summary of the Results of 102 Anoxia Tests

| | Control electro-cardiogram | Total number of tests | Positive results | | |
|---|---|---|---|---|---|
| | | | Number | Percentage | Combined percentage |
| Group 1 | Normal | 35 | 0 | 0 | 0 |
| Group 2 | Normal | 36 | 29 | 81 | 86 |
| | Abnormal | 20 | 19 | 95 | |
| Group 3 | Normal | 5 | 3 | 60 | 60 |
| | Abnormal | 0 | — | — | |
| Group 4 | Normal | 5 | 0 | 0 | |
| | Abnormal | 1 | 1 | | |

because of previous myocardial infarction. Eight tests were completed, and six were positive. No explanation can be offered for the negative test in one case, but the other patient was not suffering from anginal pain at the time of the test, and was in fact performing very heavy manual labour, so much so that he cannot have been suffering from coronary artery insufficiency at that time. His exercise test also was negative.

Group B was made up of ten patients who had no history to suggest myocardial infarction, but in each case the electrocardiogram at rest was abnormal, suggesting coronary artery insufficiency. Eleven tests were completed in this group, and each was positive (Fig. 1 and 2).

Group C comprised fourteen patients who had normal or only slightly abnormal electrocardiograms when at rest. In each case the clinical story was suggestive of angina pectoris, but other sources of pain were present, such as cervical spondylosis, hiatus hernia, peptic ulcer, chest wall injury, etc. Nineteen anoxia tests were completed on thirteen of these patients, and fifteen were positive. Taken as a whole, however, the test was positive at least once in twelve out of the thirteen patients (Fig. 3 and 4). The one patient in whom the tests were negative had a very dubious history of anginal pain and a proven duodenal ulcer; his second test, performed six months after the first, was done when he had suffered no pain for six months, and when he was seen some three years later no more discomfort had occurred; it is very likely, therefore, that in this case the test was correct and there was, and had not been, any coronary insufficiency.

Group D included nineteen patients who were similar to Group C except that no alternative source could be found for their chest pains. Eighteen tests were completed, and sixteen were positive (Fig. 5 and 6). One of the two negative tests was done on a patient whose angina had been relieved by mitral valvotomy, the pre-operative test being positive. The other test which was negative occurred in a patient in whom the history was entirely typical of angina pectoris, and a positive anoxia test had been confidently predicted.

In Group C, the test proved of great value. It established the presence of coronary insufficiency in twelve out of thirteen patients in whom the disability was thought to exist, and it was negative on two occasions when used on a patient where the clinical diagnosis of angina pectoris was almost certainly wrong.

Group D was also of great interest. The patient with mitral stenosis and angina pectoris had a positive test before valvotomy relieved her symptoms, the anoxia test becoming negative with the improvement in the clinical state. Only one did not have a positive test, and the others had at least one positive test establishing the presence of coronary insufficiency. Table III summarizes the findings in subgroups A, B, C, and D.

Returning to the other groups of patients, Group 3 comprised seven patients with intermittent claudication, none of whom would admit to any chest pain. Anoxia tests were completed on five

and there was a positive result in three. In addition, three patients in Group 2 had claudication pains accompanying their angina pectoris, and in each of them the anoxia test was positive. In none of these cases was it possible to perform exercise tests, and it is in these circumstances that the anoxia test has a great advantage over the exercise test.
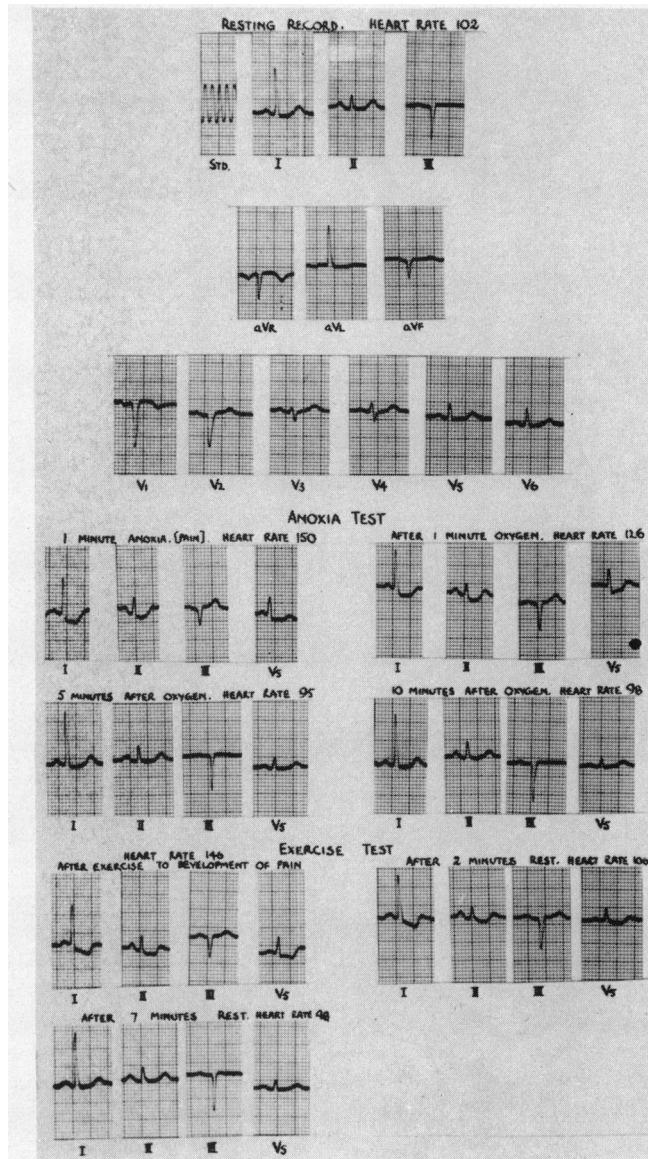


FIG. 1.—Women, domestic worker, aet. 45. Complained of left submammary pain for three years. Regarded as neurotic, and given E.C.T. B.P. 155/95, heart size and sounds normal. Anoxia test stopped after one minute because of substernal pain. Test positive, with total RS–T deviation of 6 mm. (criterion 1), and T wave reversal with RS–T deviation of more than 1 mm. in lead I (criterion 2). Exercise test produced inversion of T1 and TV5 with total RS–T segment deviation of 4 mm. This test was positive also.
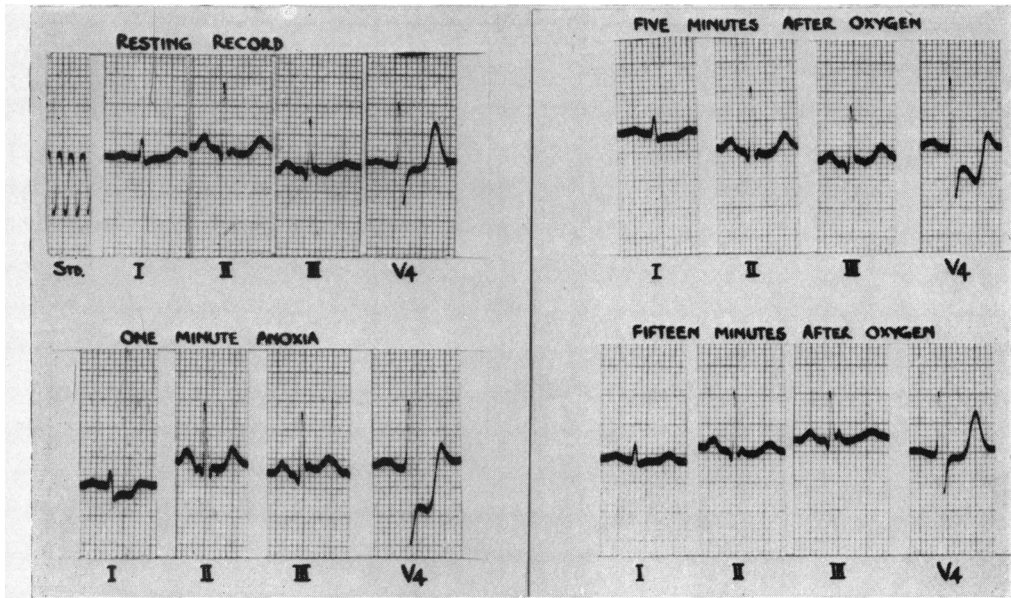
Fig. 2.—Man, aet. 59, electrician's mate. Substernal pain for twelve months, brought on by exercise, but present also after meals, relieved by alkalies. Exercise test at onset of pain was negative, and barium meal showed duodenal ulcer. B.P. 160/90. Heart size and sounds normal. Anoxia test stopped after one minute because of substernal pain. Total RS–T segment deviation of 2·0 mm. (criterion 2) and reversal of TV4 (criterion 3).
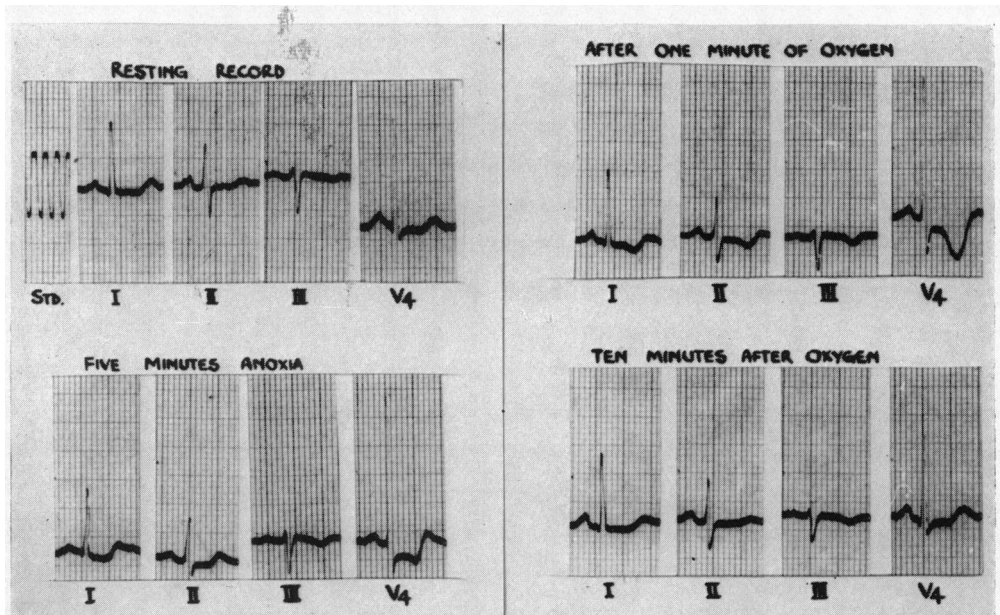


Fig. 3.—Housewife, aet. 62, Epigastric pain for two years, worse after exercise and after meals, relieved by alkalies and not by nitrites Heart size and sounds normal, B.P. 140/90. Barium meal showed a duodenal ulcer. Anoxia stopped at five minutes because of cardiographic change and slight substernal pain. The test was positive, with total RS–T segment deviation of 4·5 mm. partial inversion of T1 with RS–T deviation of 1 mm. and complete inversion of TV4. She died in a paroxysm of pain six months later.

TABLE III

RESULTS OF ANOXIA TESTS IN 53 PATIENTS WITH SUSPECTED CORONARY INSUFFICIENCY

| Group 2 Subgroups | Number of completed tests | Number of positive tests | Number of patients | Number of patients with at least one positive test |
|---|---|---|---|---|
| A | 8 | 6 | 7 | 5 |
| B | 11 | 11 | 8 | 8 |
| C | 19 | 15 | 13 | 12 |
| D | 18 | 16 | 17 | 16 |
| Totals .. | 56 | 48 | 45 | 41 |

Included in Group 4 were five patients who had symptoms and X-ray confirmation of diaphragmatic hiatus hernia. In none of these were the symptoms suggestive of coronary insufficiency, and the anoxia tests completed on three of them were all negative. In contrast to this, four patients in Group 2 also had radiologically proven hiatus herniæ, but symptoms suggestive of true angina pectoris. The anoxia test was positive in each, thus supporting the clinical impression that hiatus hernia alone does not produce anginal pain. If the defect is present and the patient has angina, he or she has also coronary insufficiency. The anoxia test was completed on one patient in Group 4 who had mitral stenosis without angina, and it was negative. Six in Group 2 had mitral valve disease with angina, and the test was positive in each.

Two patients had anoxia tests performed in an effort to elucidate the ætiology of fainting attacks. One had attacks that were thought to be non-organic, and his anoxia and exercise tests were negative. The other was suspected of having Stokes-Adams syncope, but he was never observed in an attack, and his resting cardiogram was only slightly abnormal. His anoxia test was strikingly positive although he had no chest pain, no clouding of consciousness, and no change in cardiac rhythm (Fig. 7); the diagnosis of coronary insufficiency was confirmed later at a coroner's necropsy.

Of the fifty-two tests that were positive, nineteen became so after two minutes anoxia or less; twenty-seven at between five and ten minutes anoxia, and only one after the anoxia had ceased. Table IV summarizes the relative frequency of the criteria of abnormality, the figures being similar to those of Weintraub and Bishop (1947) and of Levy *et al.* (1941). These figures confirm the view

TABLE IV

SHOWING RELATIVE FREQUENCY OF THE CRITERIA OF ABNORMALITY IN THE ANOXIA TEST

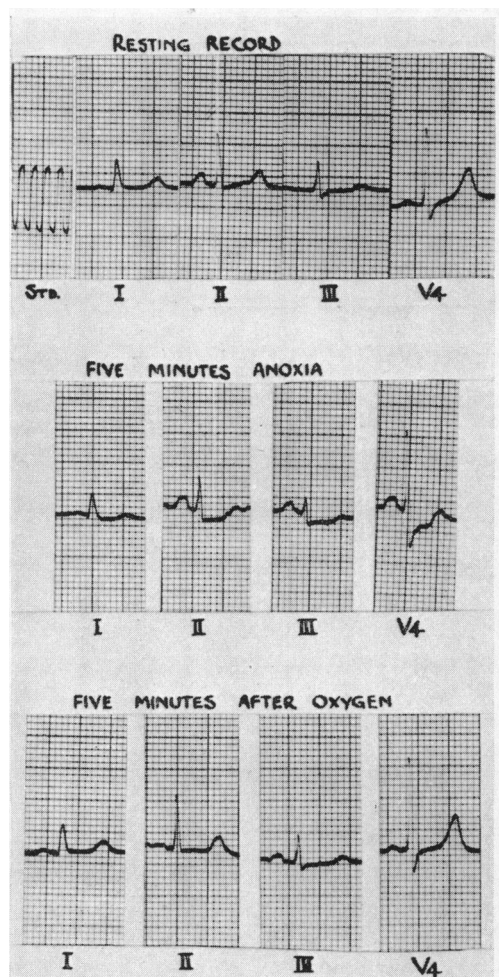| Criterion | Number of tests | Percentage of total positive tests |
|---|---|---|
| 1 Alone .. .. | 37 | 73 |
| Alone or combined | 49 | 96 |
| 2 Alone .. .. | 0 | 0 |
| Alone or combined | 7 | 13·7 |
| 3 Alone .. .. | 2 | 3·8 |
| Alone or combined | 11 | 21·6 |
| 1 and 2 .. .. | 3 | 5·8 |
| 1 and 3 .. .. | 5 | 9·7 |
| 2 and 3 .. .. | 0 | — |
| 1, 2, and 3 .. .. | 4 | 7·7 |

FIG. 4.—Housewife, aet. 47. In 1952 angina pectoris diagnosed on the history, no abnormal physical signs were present. Four years later the pain had been distorted by a gross anxiety overlay and the presence of a gastric ulcer. Still no abnormal cardiovascular signs, and B.P. normal. Anoxia test was positive, with total RS–T segment deviation of 5·5 mm. No pain occurred.
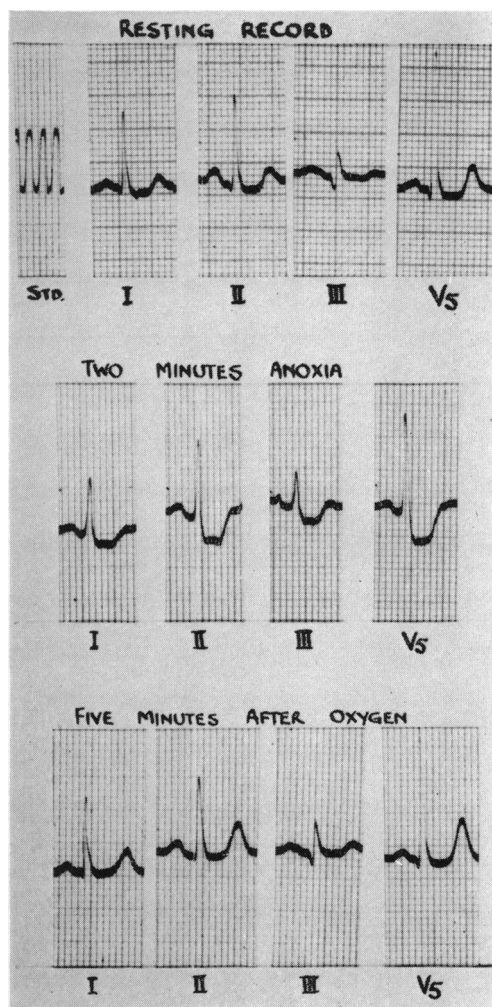
FIG. 5.—Housewife, aet. 51. Severe epigastric and lower substernal pain coming on after minimal effort, referred to left arm, left thigh and knee. B.P. 140/90, heart size and sounds normal. Anoxia test was positive (criteria 1 and 2), with total RS–T segment deviation of 12·5 mm. coinciding with slight substernal pain. The patient died six months after the test, in a sudden paroxysm of pain. No autopsy was done.

of Turner and Morton (1952) that RS–T segment deviation was the most constant and reliable finding in the anoxia test. Fig. 8 depicts the total RS–T segment deviation in all four leads, in the control series and in the abnormal patients. It shows that the maximum of 2·5 to 2·9 mm. for a normal test is correct, and that 3·0 mm. and above is probably correct for those patients with coronary insufficiency. The maximum RS–T segment change occurred most frequently in the præcordial lead, being more than three times as often as in the other leads together, in the patients with positive tests.

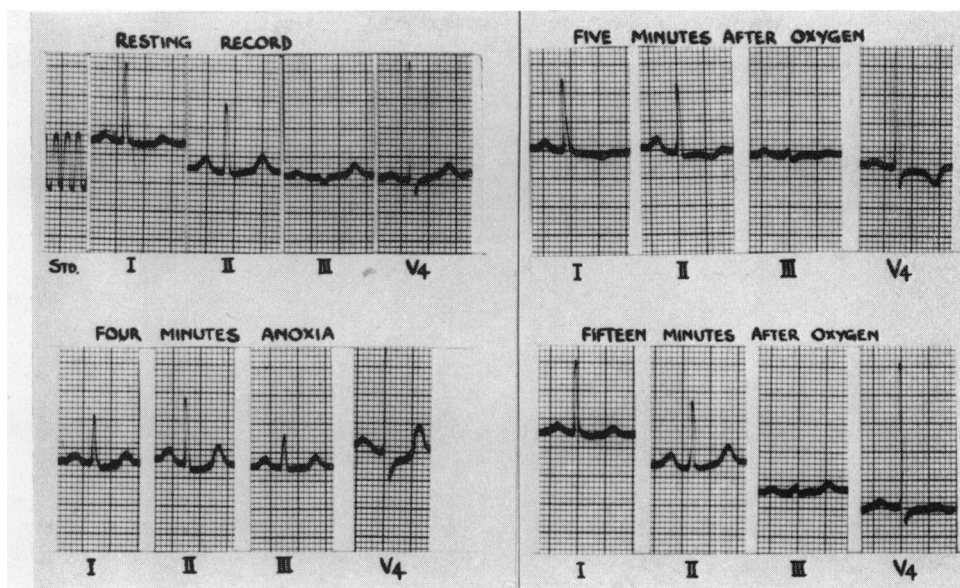The heart rate increased on an average by 26 beats a minute in the control series, and by 32

FIG. 6.—Housewife, aet. 46. History of typical angina pectoris for twelve months, with no abnormal physical signs. B.P. 130/80. Anoxia test stopped at 4 minutes because of substernal pain. Total RS–T segment deviation 4·5 mm. (criterion 1), reversal of T1 and TV4 after the anoxia was stopped, with a slow recovery rate. RS–T segment deviation of 1 mm. in lead 1 with reversed T wave constitutes criterion 2, and the reversal of TV4 criterion 3.
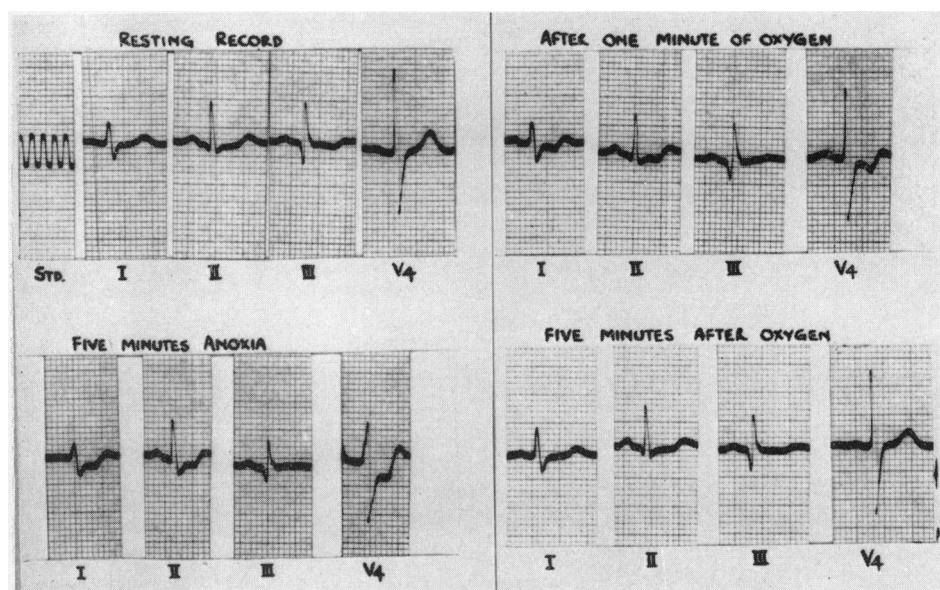


FIG. 7.—Man, aet. 54, motor driver. No chest pain, but attacks of syncope when pulse rate alleged to fall to 40 a minute. Normal heart size and sounds, B.P. 155/90, negative clinical examination. Anoxia test stopped at five minutes because of gross cardiographic change. No pain occurred. Note the tracings are half sensitivity, and allowing for this, RS–T deviation was equivalent to 13·0 mm. (criterion 1); T1 was reversed with RS–T deviation of more than 1 mm. (criterion 2); TV4 was completely reversed (criterion 3).
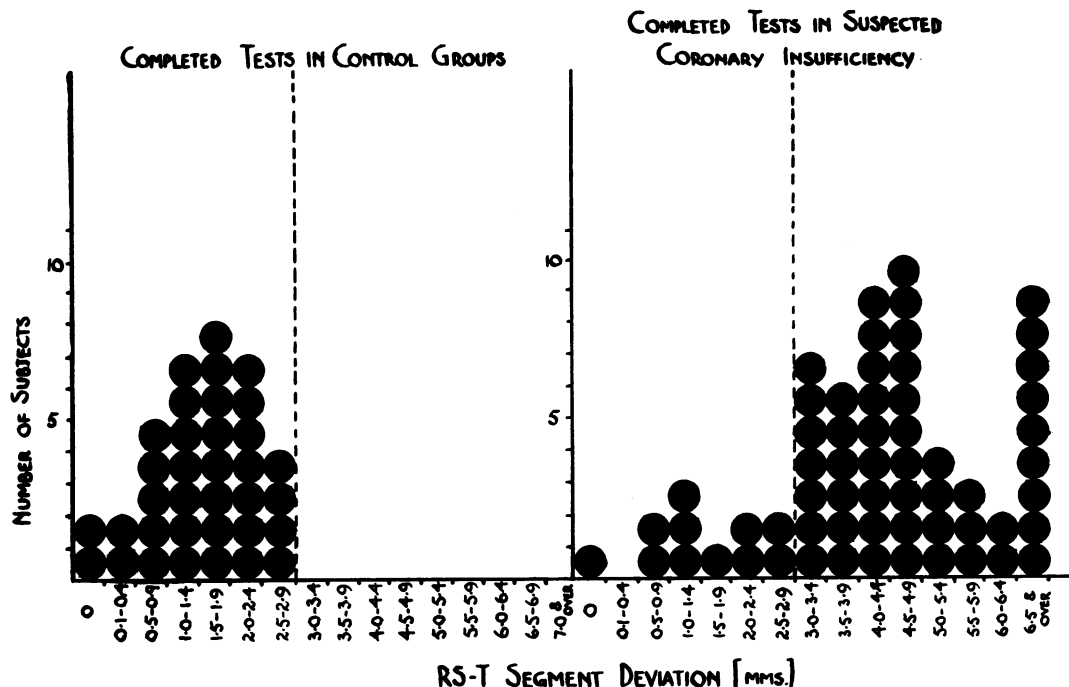
FIG. 8.—Total RS–T segment deviation in control series and in patients with coronary insufficiency.

beats a minute in the series under test, but the increase in rate bore no relation to the outcome of the test. Unless T wave changes amounted to total reversal in lead I or the præcordial lead, they also had no relation to the outcome of the test. No T wave reversal occurred in lead II unless it was present in lead I also, and when present in lead III it had no relation to the result of the test.

Prolongation of the P–R interval occurred in only one case, alternating ventricular extrasystoles in one, and a wandering pacemaker in a third. These were the only instances of either conduction defects or arrhythmias in this series, and previous investigations have also found such occurrences uncommon. Roehm *et al.* (1952) devised a method of calculating what was referred to as the "anoxæmia index" in this type of test. This depended upon the prolongation of the QT interval in patients with coronary insufficiency being made greater in the anoxia test. The index was worked out on all the patients in this series, but the difficulties of measuring the QT interval are well known, and the results of the calculations in this series showed an equal number of positive and negative indices in the control patients and in the abnormal group.

Exercise tests were performed on eleven patients for comparison with the anoxia test. In one the anoxia test was positive when the exercise test was negative—this patient had a myocardial infarction some twelve months later. The exercise test was never positive when the anoxia test was negative; five patients had both tests positive. When pain was provoked in the exercise test, it invariably lasted longer than with the anoxia test, there being no oxygen ready to relieve the symptoms.

Since the investigation began, six of the patients are known to have died. None of these was in the control group, and three who died suddenly were certified as having coronary thromboses, but no autopsies were performed. Autopsies were carried out on the other three. One man of 62 died in a paroxysm of pain, autopsy showing a recent septal infarct, with gross coronary atherosclerosis, and areas of mainly subendocardial fibrosis in the left ventricle. Another died two years after the anoxia test had been done, and was shown at autopsy to have an unsuspected

calcific aortic stenosis, much coronary artery thickening, and a recent intramural infarct, but no evidence of subendocardial fibrosis. The third patient died suddenly, some six months after having a positive anoxia test: he had complained of recurrent syncopal attacks, in one of which he was found to have a very slow pulse, but at no time did he complain of any chest pain. He died in one of the attacks, and the necropsy showed widespread severe coronary atherosclerosis, with diffuse myocardial fibrosis, much of it being subendocardial.

### ELECTROCARDIOGRAPHIC CHANGES IN THE ANOXIA TEST

The predominant abnormality produced, namely RS–T segment depression, for a long time has been known to occur also in spontaneous paroxysms of angina, and Parkinson and Bedford (1931), and Wilson and Johnston (1941) pointed out that similar changes of a more permanent nature occurred with coronary occlusion, the underlying cause being presumably of a like nature in each case, but temporary in one and permanent in the other. Brow and Holman (1934) reported that similar cardiographic records had been obtained in patients who had spontaneous attacks of angina, and in animals subjected to progressive anoxia.

Riseman *et al.* (1940) produced similar records in patients with anginal pain precipitated by exercise or anoxia, and found that the inhalation of oxygen could delay the onset of the changes in the cardiogram precipitated by exercise. Records during attacks of anginal pain have also been recorded by Bousfield (1918), Feil and Siegel (1928), Wood *et al.* (1931), Hall (1932), Turner (1933), Shapiro and Smyth (1937–8), Bryant and Wood (1947), and Scherf and Boyd (1948), and nearly all showed predominant RS–T segment depression in the standard leads, and in the præcordial lead when the latter were recorded.

Similar tracings are shown in Fig. 9, from a woman aged 71. She had typical angina on effort, but the upper record was taken when she had a short attack of pain, whilst lying at rest. The
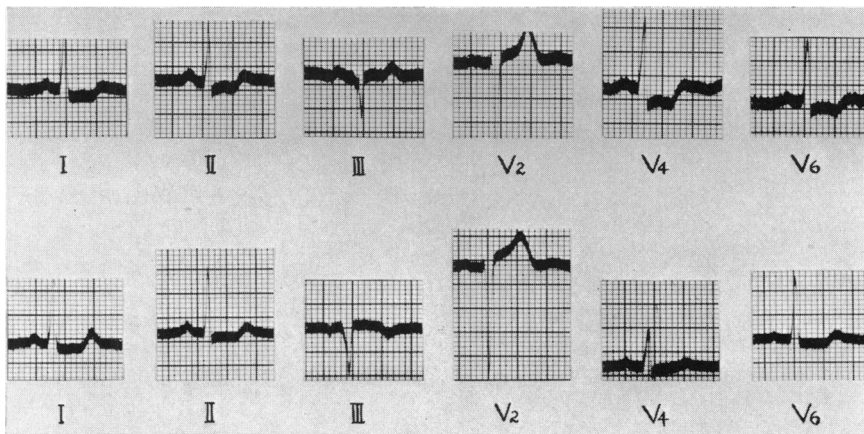


FIG. 9.—The upper record was taken during a paroxysm of anginal pain, the lower record twenty four hours later, when no pain was present.

lower record was taken twenty-four hours later, and although it is still abnormal, the marked RS–T segment depression in leads I, V4, and V6 has largely disappeared.

Myocardial anoxia produced by severe anæmia can produce records identical with those seen in the anoxia test. Fig. 10 shows the electrocardiogram of a woman, aged 52, taken half an hour before she died as a result of a massive intraperitoneal hæmorrhage. The gross RS–T segment depression was unaccompanied by any macroscopic change in the heart, and the coronary arteries were normal.

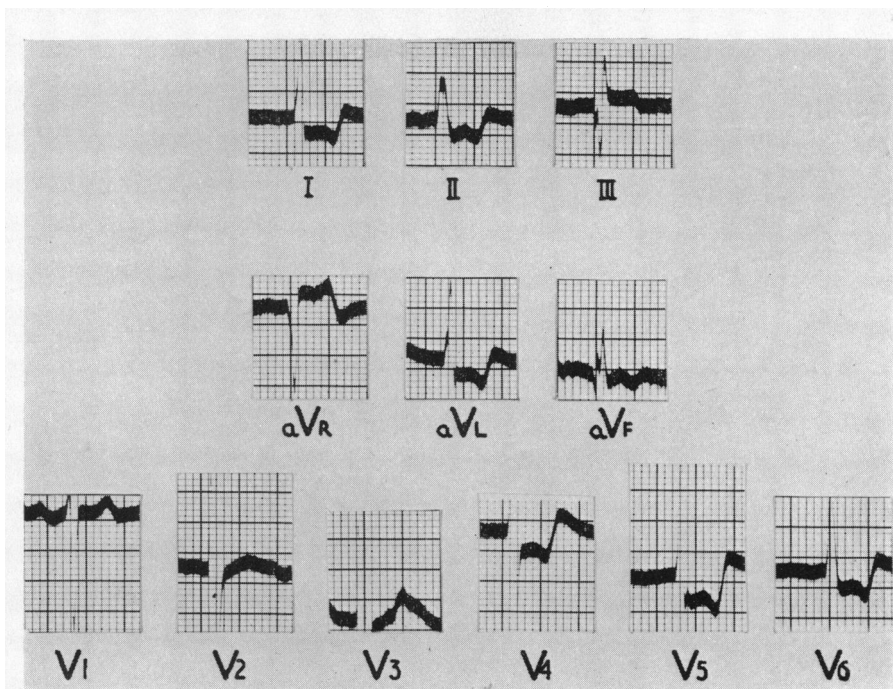Master *et al.* (1941) describing the clinical, electrocardiographic, and autopsy findings in cases

FIG. 10.—Electrocardiogram taken from a patient with severe anæmia, half an hour before death.

of acute coronary insufficiency, demonstrated again the presence of RS–T segment depression and correlated it with the "diffuse foci of myomalacia, usually mainly subendocardial, in the papillary muscles of the left ventricle and the interventricular septum." Thomson and Feil (1944), Price and Janes (1943), Bailey (1946), and Pirani and Schlichter (1946) have recorded similar RS–T depression found in patients who at autopsy were shown to have subendocardial infarcts; and experimental production of endocardial damage has the same result (Boyd and Scherf, 1940; Wolferth *et al.*, 1945; Pruitt and Valencia, 1948). The theoretical concept of these patterns has been expounded by Bayley (1943, 1944, and 1946).

It is probable therefore that the RS–T segment depression occurring in spontaneous angina, anæmia, and the exercise and anoxia tests is due to subendocardial muscle damage. Biorck (1948–9) suggested that this damage occurs because the subendocardial muscle is the last to receive its oxygen supply from the penetrating branches of the coronary arteries, and is probably sensitive to oxygen lack.

T wave changes alone have been relatively uncommon in all the published series of anoxia tests, but in this present series, they have occurred in the patients who appeared more severely affected, and when present, they have persisted longer than RS–T segment changes. It is likely that they represent more advanced coronary insufficiency but there is no proof of this.

## DISCUSSION

Greene and Gilbert (1921 and 1922) demonstrated that sufficient anoxia will produce cardiographic abnormalities even in healthy subjects, but the different types of anoxia tests have been designed to produce characteristic and recordable changes in as many pathological cases as possible, while causing no change of significance in normal subjects. Dietrich and Schwiegk (1933), using a mixture containing about 8 per cent oxygen in nitrogen, were able to produce abnormal cardiographic patterns in 35 out of 45 patients with heart disease. Rothschild and Kissin (1933) found a mixture of 6 per cent oxygen in nitrogen caused their patients

to lose consciousness, and reverted to an unsatisfactory rebreathing technique, as did Katz *et al.* (1934), whereby the test could never be properly standardized. Larsen (1936) used a 9 per cent oxygen in nitrogen mixture, and produced 13 positive tests among 30 subjects with coronary disease. The same mixture has been used by Mannheimer *et al.* (1946, 1948) who have found the test useful in the assessment of certain types of congenital heart disease.

Levy and his associates have performed many hundreds of anoxia tests using a mixture of 10 per cent oxygen in nitrogen, the patient breathing the gas for a maximum of twenty minutes. They found that the presence of a positive test bore no relationship to the levels of blood oxygen at the time, these varying from 67 to 83 per cent saturation; this work has been confirmed by Mathers and Levy (1950). However, Levy could only produce 55 per cent positive tests in subjects with coronary disease, and suggested that the production of pain without cardiographic abnormality should be regarded as a presumptive positive test. Similar figures were produced by Patterson *et al.* (1942) and Pruitt *et al.* (1945) but no false positive tests were found. Weintraub and Bishop (1947) alleged that reactions denoting ischæmia occurred in nine out of two hundred healthy people, but in fact none of these nine could be regarded as normal controls.

Penneys and Thomas (1948, 1950) attempted to modify the test by producing a more constant and standard lowering of the arterial oxygen level, but it made the test very difficult to perform, and did nothing to modify the established criteria of abnormality. Hecht (1949) used a mixture of 10 per cent oxygen, 3 per cent carbon dioxide, and 87 per cent nitrogen, and was able to produce a positive test in 74 per cent of his patients with angina pectoris, all the controls being negative. Using Levy's technique, Alexander *et al.* (1950) could produce only 33 per cent positive tests in subjects with coronary disease.

Nylin (1943), Biorck (1946 *a & b*), Lindgren (1946 *a, b, & c*) Soupanki (1948) were Scandinavian investigators whose results were essentially similar to those of Levy and his associates. Malmstrom (1947) considered the method giving 10 per cent oxygen in nitrogen produced not only a wide variation in blood oxygen levels at the end of the test, but also a very variable rate of fall of the oxygen level, both making standardization of the test more difficult. In addition to this, hyperventilation alkalosis could be produced, which itself could cause RS–T segment depression.

In order to produce a more rapid fall in the blood oxygen level, and to standardize the test better, Malmstrom used a mixture containing 6·5 per cent oxygen, and added 4·5 per cent carbon dioxide, to cause hyperventilation and a rapid lowering of blood oxygen, without alkalosis. He found that alveolar oxygen tension quickly reached a constant low level, there was less variation in the respiratory response, and no alteration in blood pH. No abnormal results were found in his control subjects, and eight out of thirteen patients with myocardial ischæmia had positive tests.

Master (1953) has admitted that the exercise test produces 6 per cent of positive results in patients without myocardial ischæmia, although he claims that it is positive in 95 per cent of coronary insufficiency. Nevertheless, the finding that one out of every 20 patients without this condition has a positive test detracts greatly from its value. This does not occur with the anoxia test, and none of the 35 patients in the present control series had a positive test. Moreover, with positive tests in over 90 per cent of pathological cases, Malmstrom's modification of the anoxia test has removed the greatest objection to its use, namely that only a relatively small percentage of patients with coronary insufficiency could be demonstrated to have this condition. It has other advantages: it can be used on patients who are unable to undertake physical exercise, there is constant electrocardiographic control, and oxygen is immediately available making the procedure definitely less dangerous. It must be admitted, however, that it is more time-consuming and that it cannot be used on patients with a low respiratory reserve.

Comparing the two types of test, Master *et al.* (1944) were able to produce similar records with each test on a series of cases of myocardial ischæmia. Biorck (1946) found 27 per cent of patients had positive anoxia and negative exercise tests, 18 per cent had positive exercise and negative anoxia tests, and 55 per cent had both positive. In the present series, only a small number of exercise tests were performed, and in only one case was the anoxia test positive and the exercise test negative; there were no patients with positive exercise and negative anoxia tests. It is probable that a place exists for the use of both tests, but the anoxia test is more reliable and less dangerous and should be the method of choice.

It has been proved of value when intermittent claudication prevented the performance of an exercise test. Three out of five cases showed evidence of coronary insufficiency and this type of patient had to be treated cautiously. Used in an attempt to elucidate the nature of chest pain in a patient with a hiatus hernia, it has been shown that the latter alone is insufficient to produce a positive test, which appears only when the pain is due to myocardial ischæmia, the hiatus hernia being incidental.

## SUMMARY

The modification of Levy's anoxia test as suggested by Malmstrom has been used to investigate a series of patients. It has been found satisfactory in that it increases the number of positive results in patients with coronary insufficiency to a level comparable with that obtained in the exercise test, without producing any false positive results.

Thirty-five patients with no clinical evidence of organic cardiovascular disease served as a control group, and in none was a positive anoxia test produced.

Where coronary insufficiency was known to be present or strongly suspected on clinical grounds, 56 tests were completed and 48 were positive (86%). This latter figure is misleading in that one test was performed on a patient with known coronary disease but with no symptoms of coronary insufficiency; two tests were negative and followed by a clinical course suggesting that the pain was not cardiac in origin; and one test was negative in a patient whose symptoms had been relieved by mitral valvotomy. Discounting these four tests, 48 tests were positive out of 52, or 93 per cent. Analysis showed that 41 cases out of 43 were found by the test to have coronary insufficiency in circumstances in which it was expected that the test would be positive, giving a total percentage of 95.

The test was positive in 3 out of 5 patients with intermittent claudication but no symptoms of coronary insufficiency, and was strikingly positive in one patient suspected of having Adams-Stokes syncope. It was negative in patients with diaphragmatic hiatus hernia when coincident coronary disease was not suspected.

The anoxia test is more time-consuming than the exercise test, but is simple to perform and provided reasonable care is taken, it is not dangerous; it has the advantage over the exercise test in that the patient is under continuous electrocardiographic observation, a supply of oxygen is constantly available so that the test can be stopped at once and its effects reversed very quickly. It can be used on patients who are physically incapable of exertion, and because of the absence of muscle tremor, the electrocardiographic records are better than those in the exercise test.

When graphic proof of coronary insufficiency is being sought, it is better to use the anoxia test first, but it is probable that there is a place for both types of test. Neither should be used as a routine investigation, as these methods cannot replace careful clinical assessment.

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